PATENT ABSTRACTS OF JAPAN

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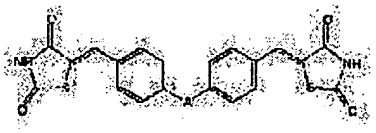
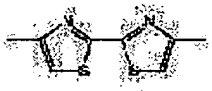
(54) NOVEL BIS-HETERORING DERIVATIVE OR SALT THEREOF

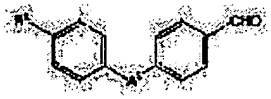


I



II

III



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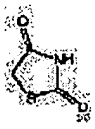


V

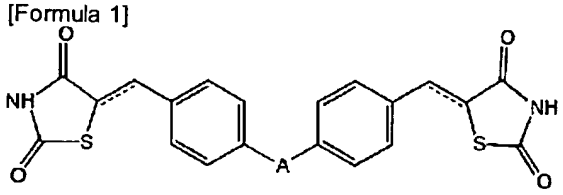
(57)Abstract:

PURPOSE: To provide a novel bis-hetero ring derivative which is useful as a prophylaxis or remedy for diabetes and a variety of complications thereof with other diseases because this derivative has hypoglycemic action with low toxicity and reduced side-effects.

CONSTITUTION: This novel bis-heteroring derivative (salt) is represented by formula I (A is a group of formula II or III, a lower alkylenedioxy group which is interrupted with a sulfur atom; the dotted line parts are each a single or double bond, respectively) and useful as a prophylaxis or remedy for diabetes, particularly insulin-independent pancreatic diabetes (type II) and a variety of complication thereof with other diseases and as a medicinal combination thereof with insulin because it has hypoglycemic action based on the insulin sensitivity- increasing action with low toxicity and reduced side-effects. This derivative is obtained by the Knoevenagel condensation reaction between an aldehyde derivative of formula IV (A3 is the same as A; R9 is formyl) and a thiazolidine derivative of formula V.

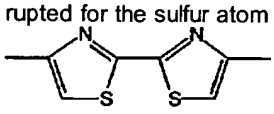
CLAIMS

[Claim(s)]
[Claim 1] The screw heterocycle derivative shown by the following general formula (I), or its salt permitted pharmaceutically.
[Formula 1]

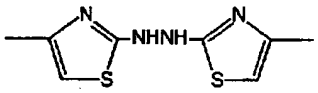


(I)

(However, each notation in a formula has the following meaning respectively.)
A: The following general formula (II), the base shown, or the low-grade alkylene dioxy machine interrupted for the sulfur atom [-izing 2]



(II)



(III)

[Formula 3]
:::::: : 単結合又は二重結合

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention] this invention relates to the physic, a new especially useful as blood-sugar fall agent (insulin sensitivity reinforcement agent) heterocycle derivative, and its salt permitted pharmaceutically.
[0002]
[Description of the Prior Art] Now, the synthetic blood-sugar fall agents currently used on clinical as a diabetic treatment agent are a sulfo nil urea agent and a ********** agent. However, since the lactic acidosis is caused, a ********** agent has a limit in the application, and is not used rarely. On the other hand, although the sulfo nil urea agent was sure and also had very few side effects, it might sometimes start the hypoglycemia and needed to pay sufficient attention in use. [blood-sugar fall]
[0003] It continues till recent years and the insulin sensitivity reinforcement agent which raises the insulin sensitivity in a peripheral organization and shows a blood-sugar fall operation attracts attention as what can be replaced with the above-mentioned synthetic blood-sugar fall agent.
[0004] this invention person etc. found out and did the patent application of having the insulin sensitivity potentiation which was excellent in screw ****** or thiazolidine derivative previously under such a situation [refer to international public presentation pamphlet of No. 93/03021 (1993)].
[0005]
[Problem(s) to be Solved by the Invention] Although various researches have been conventionally

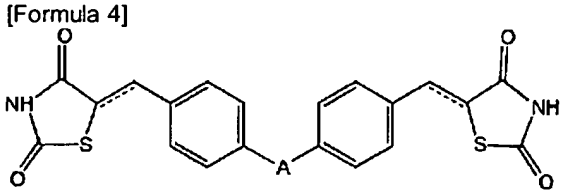
made like the above, an invention of the new insulin sensitivity reinforcement agent which was excellent in addition also in present is an important technical probrem on the medicine. And this invention person etc. completed this invention, as a result of inquiring zealously about the new compound which has an insulin sensitivity potentiation.

[0006]

[Means for Solving the Problem] That is, this invention relates to the new heterocycle derivative shown by the following general formula (I).

[0007]

[Formula 4]

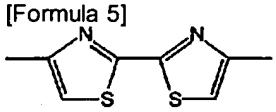


(I)

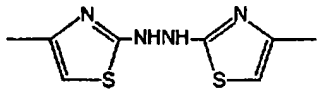
[0008] (However, each notation in a formula has the following meaning respectively.)

A: The following general formula (II), the base shown, or the low-grade alkylene dioxy machine interrupted for the sulfur atom [0009]

[Formula 5]



(II)



(III)

[0010]

[Formula 6]

┅┅ : 単結合又は二重結合

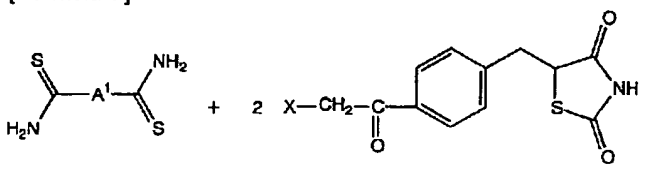
[0011] Hereafter, it explains in full detail per this invention compound. Unless especially the vocabulary that it "low-grade" Comes to set to a definition of the general formula of this specification is refused, a carbon number means 1, ten straight chains, or the chain of the letter of branching. Among these, 4, eight straight chains, or the chain of the letter of branching has a desirable carbon number.

[0012] Moreover, "the low-grade alkylene dioxy machine interrupted for the sulfur atom" Being interrupted by two sulfur primitive is desirable. specifically For example, 3, 5-dithia heptane -1, a 7-diyl-dioxy machine, 3, 6-dithia octane -1, a 8-diyl-dioxy machine, 3, 7-dithia nonane -1, a 9-diyl-dioxy machine, 3, 8-dithia decane -1, a 10-diyl-dioxy machine, etc. are mentioned.

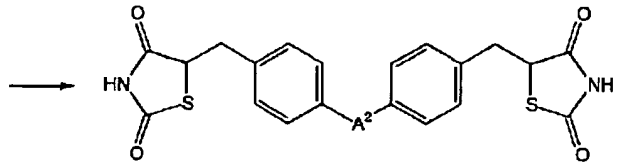
[0013] Among this invention compound (I), since the compound which has 2 and 4-dioxo thiazolidine ring has an acid proton to the ring, it can form the salt with a base. The salt of a compound (I) permitted pharmaceutically is included by this invention, and the salt with organic bases, such as the salt with inorganic bases, such as trivalent metals, such as alkaline earth metal, such as alkali metal, such as a lithium, sodium, and a potassium, magnesium, and calcium, and aluminum, a monomethylamine, an ethylamine, a dimethylamine, a diethylamine, a trimethylamine, a triethylamine, a monoethanolamine, a diethanolamine, a triethanolamine, a cyclohexylamine, a lysine, and an ornithine, be mentioned to it as such a salt

[0014] A tautomer exists according to the modality of A ring machine of this invention compound. Moreover, according to the modality of substituent, it may have a double bond or an asymmetric carbon atom, and a geometrical isomer and an optical isomer exist based on those presence. All of the things from which these isomers were isolated, and mixture are included by this invention.

[0015] Furthermore, this invention compound (I) and its salt may be isolated as matter of a crystal polymorphism as a hydrate and various kinds of solvates, and the various solvates permitted pharmaceutically, such as these hydrates and ethanol ****, or the matter of a crystal polymorphism is also contained in this invention.
[0016] (Manufacturing method) this invention compound uses the basic skeleton or the characteristic feature based on the modality of substituent, and can compound it with the application of various synthesis methods. The typical process is illustrated below.
[0017] The 1st process [0018]
[Formula 7]

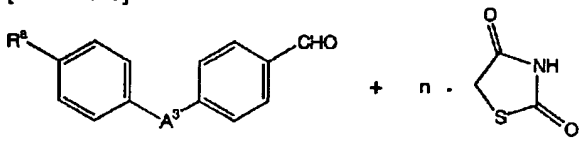


(IV) (V)

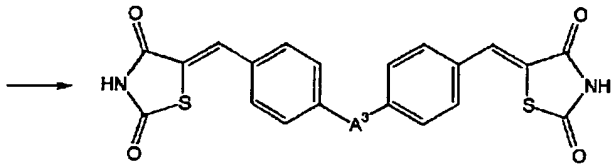


(Ia)

[0019] (A1 means among a formula the base shown by single bond or formula-NHNH-, and A2 means the above-mentioned general formula (II) or (III) the base shown.) X shows a leaving group and is specifically a halogen atom.
The compound shown by the general formula (Ia) can be manufactured among this invention compound (I) by adding the compound shown by the general formula (V) of twice [compound / which is shown by the general formula (IV)], or a superfluous mol.
[0020] the inside of the organic solvents with a reaction inactive for reactions, such as chloroform, methylene chloride, ethylene chloride, a tetrahydrofuran, diethylether, a diisopropyl ether, a dioxane, dimethoxyethane (monochrome ******), the screw (2-methoxy ethyl) ether (jig rim), a methanol, ethanol, the 2-ethoxyethanol (tradename:cellosolve), 2-methoxy ethanol (tradename:methyl cellosolve), dimethyl sulfoxide, and a sulfo run, or these mixed solvents, a room temperature, or warming – it is advantageous to carry out in the
[0021] The 2nd process [0022]
[Formula 8]



(VII) (VIII)



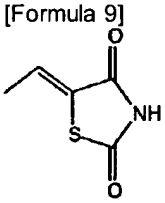
(Ib)

[0023] (A3 means among a formula the low-grade alkylene dioxy machine interrupted for the sulfur atom, and Ra means the base shown by the formyl machine or the following general formula (VI).)

Moreover, n is Ra. When it is a formyl machine, it is 2, and it is 1 when other.

[0024]

[Formula 9]



(VI)

[0025] The heterocycle derivative shown by the general formula (Ib) is manufactured by the general condensation reaction (Knoevenagel condensation) to which the thiazolidine derivative shown by the monochrome or screw aldehyde derivative shown by the general formula (VII), and the formula (VIII) is made to react.

[0026] A condensation reaction is performed under presence of bases, such as alkali-metal alcoholates, such as acetic-acid-piperidine mixture, the beta-alanine, an alumina, a titanium tetrachloride, a tin tetrachloride, a boron trifluoride, a potassium fluoride, an ammonium chloride, a sodium hydroxide, a potassium hydroxide, a sodium carbonate, an ammonium acetate, a sodium ethoxide, and potassium t-butoxide, a diethylamine, a triethylamine, pentylamine, and a pyridine. In organic solvents, such as alcohol, such as ethanol and a methanol, a tetrahydrofuran, diethylether, methylene chloride, chloroform, benzene, toluene, an acetonitrile, an acetic acid, and a propionic acid, water, or these mixed solvents, a compound (VII) and a compound (VIII) are used from a grade mol or 2 double mol, one side is mostly used as mist or an excessive amount from the chemical equivalent, and it is suitable to carry out to the bottom of heating preferably under a room temperature or heating.

[0027] Thus, the manufactured this invention compound is isolated and refined as a disengagement compound, its salt, a hydrate, various solvates, etc. The salt of this invention compound (I) permitted pharmaceutically can also be manufactured by giving a usual salt-formation reaction.

[0028] Isolation refining is performed with the application of usual chemistry operations, such as an extraction, fractional-crystallization-izing, and various fractionation chromatographies.

[0029] A tautomer and a geometrical isomer are separable using the difference of the physical chemistry-property between the thing for which a suitable raw material is chosen, or an isomer.

[0030] moreover -- an optical isomer -- being suitable -- a raw material -- a compound -- choosing -- things -- or -- a racemic compound -- an optical resolution -- a method -- [-- for example, -- being general -- optical activity -- a base -- diastereomeric salt -- leading -- optical resolution -- carrying out -- technique -- etc. --] -- an isomer pure in stereochemistry -- it can lead .

[0031]

[Effect of the Invention] this invention compound (I), its salt, etc. have the outstanding blood-sugar fall operation based on an insulin sensitivity potentiation, are low toxicity, and are useful to ******** with few side effects as the prevention treatment agent of the various complications of the non-insulin-dependent diabetes mellitus (II type) or diabetes, a combined use medicine with an insulin, etc.

[0032] The outstanding blood-sugar fall operation based on the insulin sensitivity potentiation of this invention is checked by the following examining methods.

[0033] The male kk mouse of blood-sugar fall activity 4-5w came to hand from Japanese book Clare, Inc. By the high calorie diet (CMF and Oriental Yeast), the individual feeding of the animal was carried out and it was examined using the thing before and behind the weight of 40g.

[0034] From the tail vena, measurement of the blood sugar level extracted the sanguis of 10microl, performed after a deproteinization and centrifugal separation by 100micro l of 0.33 perchloric acid of N, and measured the glucose of a supernatant phase using the glucose oxidase method. The blood sugar made one group six animals 200mg / more than dl, and the examination was presented.

[0035] The medicine was suspended in the methyl cellulose 0.5%, and performed the Nikkei opening medication every time per day for four days. From the tail vena, the sanguis was extracted on medication before and the 5th, and the blood sugar was measured by the above-mentioned technique at them.

[0036] Using the support and the excipient for a tablet which are usually used, and other additives, the physic constituent which contains one sort of the compound shown by the general formula (I) or its salt permitted pharmaceutically or two sorts or more as an active principle is prepared by a tablet, powder, a fine-grain agent, a granule, a capsule, the pilule, the solution, the injection, the suppository, etc., and is prescribed for the patient taking-orally-wise or parenterally. Although the clinical dose to the Homo sapiens of this invention compound is suitably determined in consideration of a patient's symptom, weight, age, sex, etc. which are applied, it is usually 1-2000mg in adult 1 sunny taking orally, and pre-

scribes this for the patient in 1 time or several steps. Since the dose is changed on condition that various, an amount fewer than the above-mentioned dose domain may be enough as it.
[0037] A tablet, powder, a granule, etc. are used as a solid-state constituent for the internal use by this invention. In such a solid-state constituent, one or the active substance beyond it is mixed with at least one inactive diluent, for example, a lactose, a mannitol, grape sugar, hydroxypropylcellulose, a microcrystal cellulose, starch, a polyvinyl pyrrolidone, and magnesium aluminometasilicate. The constituent may contain the solubilization or ********** like additives other than an inactive diluent, for example, lubricant like a magnesium stearate and disintegrator like a calcium carboxymethyl cellulose, a stabilizing agent like a lactose, glutamic acid, or an aspartic acid according to a conventional method. You may carry out the coat of a tablet or the pilule as occasion demands with the film of stomach solubility, such as cane sugar, gelatin, hydroxypropylcellulose, and a hydroxypropyl-methylcellulose free-wheelplate rate, or the enteric nature matter.
[0038] The liquid constituent for internal use contains the inactive diluent generally used, for example, a purified water, and ethanol including the opacifier permitted in medicine, a solution agent, the suspension, the syrup, the elixir, etc. This constituent may contain solubilization or a solubilizing agent, a wetting agent, an adjuvant like the suspension, a sweetening agent, a flavor agent, an aromatic, and antiseptics in addition to an inactive diluent.
[0039] As injection for a parenteral administration, a sterile water or non-water solution agent, the suspension, and an opacifier are included. As a water solution agent and a diluent of the suspension, distilled water for injection and a physiological saline are contained, for example. As the solution agent of non-water solubility, and a diluent of the suspension, there are a propylene glycol, a polyethylene glycol, vegetable oil like olive oil, the alcohols like ethanol, polysorbate 80 (tradename), etc., for example. Such a constituent may also contain an additive still like an isotonizing agent, antiseptics, a wetting agent, an emulsifier, a dispersant, a stabilizing agent (for example, lactose), solubilization, or a solubilizing agent. These are sterility-ized by the combination or irradiation of filtration and a germicide which lets for example, a bacterium hold VCF pass. These can manufacture a sterile solid-state constituent again, and can also melt and use it for sterile water or the sterile solvent for injection before use.
[0040]
[Example] Below, an example explains this invention still in detail.
[0041] (Example 1) alpha-******-4'-[(2, 4-dioxo-5-thiazolysinyl)methyl] acetophenone 3.28g, rubeanic acid 0.6g, ethanol 20ml was agitated at the room temperature for 3 hours. Furthermore, after agitating at 70 degrees C for 3 hours, having added N-hydrochloric acid and referring to it as pH 1, the crystal was ****ed, it dried after rinsing ethanol washing, and 4, 4'-screw [- [(2, 4-dioxo-5-thiazolysinyl)methyl] phenyl]-2, and 2'-********** 1.5g was obtained. [4]
[0042] Melting point 300 degrees C Above elemental-analysis value (C26H18N4O4 S4 ******)
C(%) H(%) N(%) S(%)
Theoretical value 53.96 3.14 9.68 22.16 experimental values 53.47 3.18 9.50 22.14 mass-analysis value (m/z):577[(M-H)-] FAB nuclear-magnetic-resonance spectrum (DMSO-d6, TMS internal standard)
delta: 2.10 (2H, dd), 3.44 (2H, dd), 4.97 (2H, dd), 7.36 (4H, dd), 7.96 (4H, dd), 8.31 (2H, s), 12.05 (2H, bs)
(Example 2) alpha-******-4'-[(2, 4-dioxo-5-thiazolysinyl)methyl] acetophenone 3.28g, 2, 5-dithio ******** 0.75g and ethanol 20ml were agitated at the room temperature for 3 hours. furthermore, a crystal after agitating at 50 degrees C for 3 hours – ****ing – ethanol washing – carrying out – 1 and 2-screw [4 - [- [(2, 4-dioxo-5-thiazolysinyl)methyl] phenyl]-2-thiazolyl] hydrazine hydrobromate 1.2g was obtained. [4]
[0043] Decomposition point 170 degrees C Above elemental-analysis value (C26H20N6O4 S4+HBr ******)
C(%) H(%) N(%) S(%)
Theoretical value 45.28 3.07 12.19 18.60 experimental values 45.02 3.21 11.88 18.33 mass-analysis value (m/z):609[(M+H)+] FAB/Pos
Nuclear-magnetic-resonance spectrum (DMSO-d6, TMS internal standard)
delta:3.15 (2H, dd), 3.44 (2H, dd), 4.95 (2H, dd), 7.30 (4H, dd), 6.753 (2H, b) and 7.77 (4H, dd), and 9.5- 10.05 (1H, b) and 12.05 (2H, bs)
(Example 3) 1, 8-dichloro -3, 6-dithia octane 1.8g, 2.2g of anhydrous potassium carbonate, 4-hydroxy benzaldehyde 2g and dimethylformamide 20ml were agitated at 70 degrees C for 12 hours. 20ml of water is added after a reaction end, a crystal is ****ed, and it is water. 50ml, methanol It washes by 10ml and is 1 and 8-screw (4-formyl phenoxy). - 3, 6 ******** octane 2g was obtained.
[0044] 1, the 8-screw (4-formyl phenoxy) -3, 6-dithia octane which were obtained above 1g, 2, 4-thiazolidinedione 0.5g, ammonium acetate 10mg, acetic acid The heating reflux of the 50ml was car-

ried out for 24 hours. the time crystal of heat – ****ing – 50ml of water, and methanol 50ml – washing – 1, 8-screw [- [(2, 4-dioxo-5-thia **********)methyl] phenoxy]-3, and 6-dithia octane 0.5g was obtained. [4]

[0045]

C(%) H(%) N(%) S(%)

Theoretical value 53.04 4.11 4.76 21.79 experimental values 53.14 4.11 4.46 21.97 mass-analysis value (m/z):587[(M-H)-] FAB/Neg

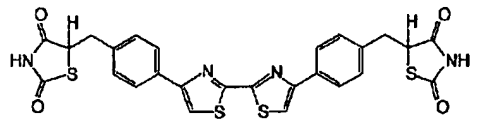
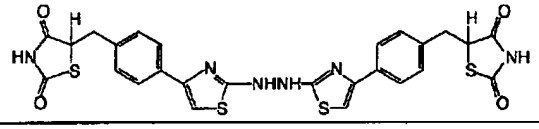
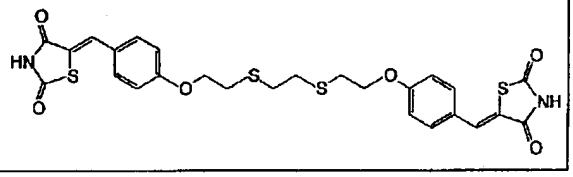
Nuclear-magnetic-resonance spectrum (DMSO-d6, TMS internal standard)

delta: 2.86 (4H, s), 2.95 (4H, t), 3.32 (4H, t), 4.22 (4H, t), 7.10 (4H, dd), 7.53 (4H, dd), 7.73 (2H, s), 12.48 (2H, bs)

The thing mentioned above [Table 1 / the chemical structure formula of the compound obtained according to the above-mentioned example].

[0046]

[Table 1]

実施例 1	
実施例 2	
実施例 3	

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Technique

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Effect

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[0034] From the tail vena, measurement of the blood sugar level extracted the sanguis of 10microl, performed after a deproteinization and centrifugal separation by 100micro l of 0.33 perchloric acid of N, and measured the glucose of a supernatant phase using the glucose oxidase method. The blood sugar made one group six animals 200mg / more than dl, and the examination was presented.
[0035] The medicine was suspended in the methyl cellulose 0.5%, and performed the Nikkei opening medication every time per day for four days. From the tail vena, the sanguis was extracted on medication before and the 5th, and the blood sugar was measured by the above-mentioned technique at them.
[0036] Using the support and the excipient for a tablet which are usually used, and other additives, the physic constituent which contains one sort of the compound shown by the general formula (I) or its salt permitted pharmaceutically or two sorts or more as an active principle is prepared by a tablet, powder, a fine-grain agent, a granule, a capsule, the pilule, the solution, the injection, the suppository, etc., and is prescribed for the patient taking-orally-wise or parenterally. Although the clinical dose to the Homo sapiens of this invention compound is suitably determined in consideration of a patient's symptom, weight, age, sex, etc. which are applied, it is usually 1-2000mg in adult 1 sunny taking orally, and prescribes this for the patient in 1 time or several steps. Since the dose is changed on condition that various, an amount fewer than the above-mentioned dose domain may be enough as it.
[0037] A tablet, powder, a granule, etc. are used as a solid-state constituent for the internal use by this invention. In such a solid-state constituent, one or the active substance beyond it is mixed with at least one inactive diluent, for example, a lactose, a mannitol, grape sugar, hydroxypropylcellulose, a microcrystal cellulose, starch, a polyvinyl pyrrolidone, and magnesium aluminometasilicate. The constituent may contain the solubilization or ********** like additives other than an inactive diluent, for example, lubricant like a magnesium stearate and disintegrator like a calcium carboxymethyl cellulose, a stabilizing agent like a lactose, glutamic acid, or an aspartic acid according to a conventional method. You may carry out the coat of a tablet or the pilule as occasion demands with the film of stomach solubility, such as cane sugar, gelatin, hydroxypropylcellulose, and a hydroxypropyl-methylcellulose free-wheel-plate rate, or the enteric nature matter.
[0038] The liquid constituent for internal use contains the inactive diluent generally used, for example, a purified water, and ethanol including the opacifier permitted in medicine, a solution agent, the suspension, the syrup, the elixir, etc. This constituent may contain solubilization or a solubilizing agent, a wetting agent, an adjuvant like the suspension, a sweetening agent, a flavor agent, an aromatic, and antiseptics in addition to an inactive diluent.
[0039] As injection for a parenteral administration, a sterile water or non-water solution agent, the suspension, and an opacifier are included. As a water solution agent and a diluent of the suspension, distilled water for injection and a physiological saline are contained, for example. As the solution agent of non-water solubility, and a diluent of the suspension, there are a propylene glycol, a polyethylene glycol, vegetable oil like olive oil, the alcohols like ethanol, polysorbate 80 (tradename), etc., for example. Such a constituent may also contain an additive still like an isotonizing agent, antiseptics, a wetting agent, an emulsifier, a dispersant, a stabilizing agent (for example, lactose), solubilization, or a solubilizing agent. These are sterility-ized by the combination or irradiation of filtration and a germicide which lets for example, a bacterium hold VCF pass. These can manufacture a sterile solid-state constituent again, and can also melt and use it for sterile water or the sterile solvent for injection before use.

TECHNICAL PROBLEM

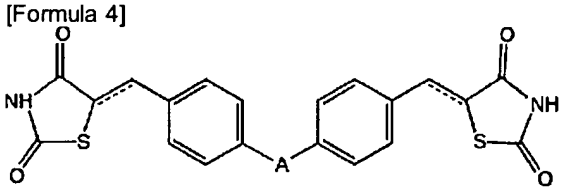
[Problem(s) to be Solved by the Invention] Although various researches have been conventionally made like the above, an invention of the new insulin sensitivity reinforcement agent which was excellent in addition also in present is an important technical probrem on the medicine. And this invention person etc. completed this invention, as a result of inquiring zealously about the new compound which has an insulin sensitivity potentiation.

MEANS

[Means for Solving the Problem] That is, this invention relates to the new heterocycle derivative shown by the following general formula (I).

[0007]

[Formula 4]

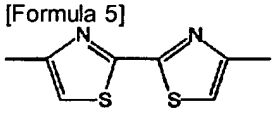


(I)

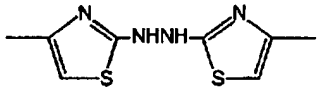
[0008] (However, each notation in a formula has the following meaning respectively.)

A: The following general formula (II), the base shown, or the low-grade alkylene dioxy machine interrupted for the sulfur atom [0009]

[Formula 5]



(II)



(III)

[0010]

[Formula 6]

: 単結合又は二重結合

[0011] Hereafter, it explains in full detail per this invention compound. Unless especially the vocabulary that it "low-grade" Comes to set to a definition of the general formula of this specification is refused, a carbon number means 1, ten straight chains, or the chain of the letter of branching. Among these, 4, eight straight chains, or the chain of the letter of branching has a desirable carbon number.

[0012] Moreover, "the low-grade alkylene dioxy machine interrupted for the sulfur atom" Being interrupted by two sulfur primitive is desirable. specifically For example, 3, 5-dithia heptane -1, a 7-diyl-dioxy machine, 3, 6-dithia octane -1, a 8-diyl-dioxy machine, 3, 7-dithia nonane -1, a 9-diyl-dioxy machine, 3, 8-dithia decane -1, a 10-diyl-dioxy machine, etc. are mentioned.

[0013] Among this invention compound (I), since the compound which has 2 and 4-dioxo thiazolidine ring has an acid proton to the ring, it can form the salt with a base. The salt of a compound (I) permitted pharmaceutically is included by this invention, and the salt with organic bases, such as the salt

with inorganic bases, such as trivalent metals, such as alkaline earth metal, such as alkali metal, such as a lithium, sodium, and a potassium, magnesium, and calcium, and aluminum, a monomethylamine, an ethylamine, a dimethylamine, a diethylamine, a trimethylamine, a triethylamine, a monoethanolamine, a diethanolamine, a triethanolamine, a cyclohexylamine, a lysine, and an ornithine, be mentioned to it as such a salt

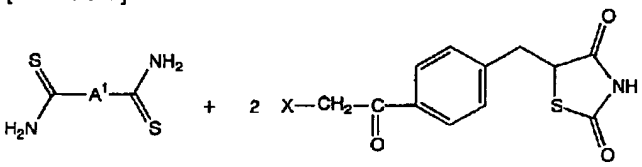
[0014] A tautomer exists according to the modality of A ring machine of this invention compound. Moreover, according to the modality of substituent, it may have a double bond or an asymmetric carbon atom, and a geometrical isomer and an optical isomer exist based on those presence. All of the things from which these isomers were isolated, and mixture are included by this invention.

[0015] Furthermore, this invention compound (I) and its salt may be isolated as matter of a crystal polymorphism as a hydrate and various kinds of solvates, and the various solvates permitted pharmaceutically, such as these hydrates and ethanol ****, or the matter of a crystal polymorphism is also contained in this invention.

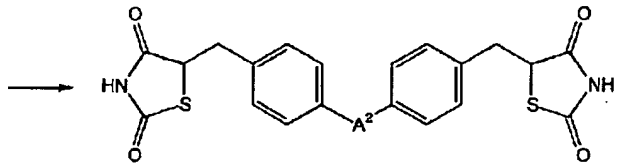
[0016] (Manufacturing method) this invention compound uses the basic skeleton or the characteristic feature based on the modality of substituent, and can compound it with the application of various synthesis methods. The typical process is illustrated below.

[0017] The 1st process [0018]

[Formula 7]



(IV) (V)



(Ia)

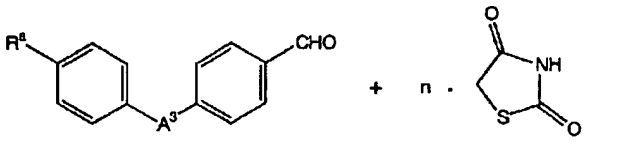
[0019] (A1 means among a formula the base shown by single bond or formula-NHNH-, and A2 means the above-mentioned general formula (II) or (III) the base shown.) X shows a leaving group and is specifically a halogen atom.

The compound shown by the general formula (Ia) can be manufactured among this invention compound (I) by adding the compound shown by the general formula (V) of twice [compound / which is shown by the general formula (IV)], or a superfluous mol.

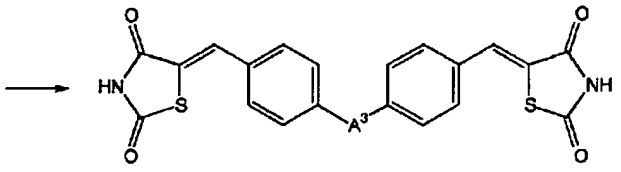
[0020] the inside of the organic solvents with a reaction inactive for reactions, such as chloroform, methylene chloride, ethylene chloride, a tetrahydrofuran, diethylether, a diisopropyl ether, a dioxane, dimethoxyethane (monochrome ******), the screw (2-methoxy ethyl) ether (jig rim), a methanol, ethanol, the 2-ethoxyethanol (tradename:cellosolve), 2-methoxy ethanol (tradename:methyl cellosolve), dimethyl sulfoxide, and a sulfo run, or these mixed solvents, a room temperature, or warming – it is advantageous to carry out in the

[0021] The 2nd process [0022]

[Formula 8]



(VII) (VIII)



(Ib)

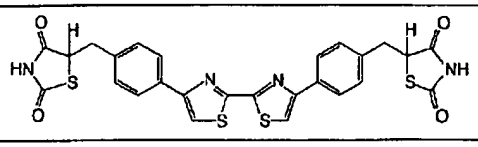
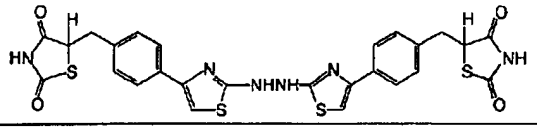
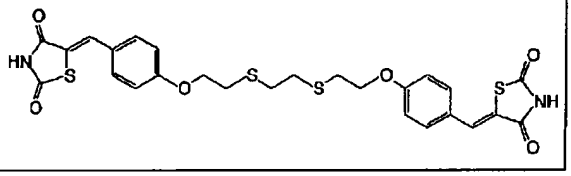
[0023] (A3 means among a formula the low-grade alkylene dioxy machine interrupted for the sulfur atom, and Ra means the base shown by the formyl machine or the following general formula (VI).) Moreover, n is Ra. When it is a formyl machine, it is 2, and it is 1 when other.
[0024]
[Formula 9]

[0025] The heterocycle derivative shown by the general formula (Ib) is manufactured by the general condensation reaction (Knoevenagel condensation) to which the thiazolidine derivative shown by the monochrome or screw aldehyde derivative shown by the general formula (VII), and the formula (VIII) is made to react.
[0026] A condensation reaction is performed under presence of bases, such as alkali-metal alcoholates, such as acetic-acid-piperidine mixture, the beta-alanine, an alumina, a titanium tetrachloride, a tin tetrachloride, a boron trifluoride, a potassium fluoride, an ammonium chloride, a sodium hydroxide, a potassium hydroxide, a sodium carbonate, an ammonium acetate, a sodium ethoxide, and potassium t-butoxide, a diethylamine, a triethylamine, pentylamine, and a pyridine. In organic solvents, such as alcohol, such as ethanol and a methanol, a tetrahydrofuran, diethylether, methylene chloride, chloroform, benzene, toluene, an acetonitrile, an acetic acid, and a propionic acid, water, or these mixed solvents, a compound (VII) and a compound (VIII) are used from a grade mol or 2 double mol, one side is mostly used as mist or an excessive amount from the chemical equivalent, and it is suitable to carry out to the bottom of heating preferably under a room temperature or heating.
[0027] Thus, the manufactured this invention compound is isolated and refined as a disengagement compound, its salt, a hydrate, various solvates, etc. The salt of this invention compound (I) permitted pharmaceutically can also be manufactured by giving a usual salt-formation reaction.
[0028] Isolation refining is performed with the application of usual chemistry operations, such as an extraction, fractional-crystallization-izing, and various fractionation chromatographies.
[0029] A tautomer and a geometrical isomer are separable using the difference of the physical chemistry-property between the thing for which a suitable raw material is chosen, or an isomer.
[0030] moreover -- an optical isomer -- being suitable -- a raw material -- a compound -- choosing -- things -- or -- a racemic compound -- an optical resolution -- a method -- [-- for example, -- being general -- optical activity -- a base -- diastereomeric salt -- leading -- optical resolution -- carrying out -- technique -- etc. --] -- an isomer pure in stereochemistry -- it can lead .

EXAMPLE

[Example] Below, an example explains this invention still in detail.
[0041] (Example 1) alpha-******-4'-[(2, 4-dioxo-5-thiazolysinyl)methyl] acetophenone 3.28g, rubeanic acid 0.6g, ethanol 20ml was agitated at the room temperature for 3 hours. Furthermore, after agitating at 70 degrees C for 3 hours, having added N-hydrochloric acid and referring to it as pH 1, the crystal was ****ed, it dried after rinsing ethanol washing, and 4, 4'-screw [- [(2, 4-dioxo-5-thiazolysinyl)methyl] phenyl]-2, and 2'-********** 1.5g was obtained. [4]
[0042] Melting point 300 degrees C Above elemental-analysis value (C26H18N4O4 S4 ******)
C(%) H(%) N(%) S(%)
Theoretical value 53.96 3.14 9.68 22.16 experimental values 53.47 3.18 9.50 22.14 mass-analysis value (m/z):577[(M-H)-] FAB nuclear-magnetic-resonance spectrum (DMSO-d6, TMS internal standard)
delta: 2.10 (2H, dd), 3.44 (2H, dd), 4.97 (2H, dd), 7.36 (4H, dd), 7.96 (4H, dd), 8.31 (2H, s), 12.05 (2H, bs)
(Example 2) alpha-******-4'-[(2, 4-dioxo-5-thiazolysinyl)methyl] acetophenone 3.28g, 2, 5-dithio ******** 0.75g and ethanol 20ml were agitated at the room temperature for 3 hours. furthermore, a crystal after agitating at 50 degrees C for 3 hours – ****ing – ethanol washing – carrying out – 1 and 2-screw [4 - [- [(2, 4-dioxo-5-thiazolysinyl)methyl] phenyl]-2-thiazolyl] hydrazine hydrobromate 1.2g was obtained. [4]
[0043] Decomposition point 170 degrees C Above elemental-analysis value (C26H20N6O4 S4+HBr ******)
C(%) H(%) N(%) S(%)
Theoretical value 45.28 3.07 12.19 18.60 experimental values 45.02 3.21 11.88 18.33 mass-analysis value (m/z):609[(M+H)+] FAB/Pos
Nuclear-magnetic-resonance spectrum (DMSO-d6, TMS internal standard)
delta:3.15 (2H, dd), 3.44 (2H, dd), 4.95 (2H, dd), 7.30 (4H, dd), 6.753 (2H, b) and 7.77 (4H, dd), and 9.5- 10.05 (1H, b) and 12.05 (2H, bs)
(Example 3) 1, 8-dichloro -3, 6-dithia octane 1.8g, 2.2g of anhydrous potassium carbonate, 4-hydroxy benzaldehyde 2g and dimethylformamide 20ml were agitated at 70 degrees C for 12 hours. 20ml of water is added after a reaction end, a crystal is ****ed, and it is water. 50ml, methanol It washes by 10ml and is 1 and 8-screw (4-formyl phenoxy). - 3, 6 ******** octane 2g was obtained.
[0044] 1, the 8-screw (4-formyl phenoxy) -3, 6-dithia octane which were obtained above 1g, 2, 4-thiazolidinedione 0.5g, ammonium acetate 10mg, acetic acid The heating reflux of the 50ml was carried out for 24 hours. the time crystal of heat – ****ing – 50ml of water, and methanol 50ml – washing – 1, 8-screw [- [(2, 4-dioxo-5-thia **********)methyl] phenoxy]-3, and 6-dithia octane 0.5g was obtained. [4]
[0045]
C(%) H(%) N(%) S(%)
Theoretical value 53.04 4.11 4.76 21.79 experimental values 53.14 4.11 4.46 21.97 mass-analysis value (m/z):587[(M-H)-] FAB/Neg
Nuclear-magnetic-resonance spectrum (DMSO-d6, TMS internal standard)
delta: 2.86 (4H, s), 2.95 (4H, t), 3.32 (4H, t), 4.22 (4H, t), 7.10 (4H, dd), 7.53 (4H, dd), 7.73 (2H, s), 12.48 (2H, bs)
The thing mentioned above [Table 1 / the chemical structure formula of the compound obtained according to the above-mentioned example].
[0046]

[Table 1]

实施例 1	
实施例 2	
实施例 3	

[Translation done.]